Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-9, 11-12, 14-15, 17-18, 20, 37-40, 43-64 are pending in the application, with claims 1, 2 and 47 being the independent claims. Claims 10, 13, 16, 19, 21-36, and 41-42 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Support for the amendments can be found at least in the cancelled claims and throughout the specification. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objections to the Drawings

A Notice of Draftsperson's Patent Drawing Review (PTO-948) was mailed together with the present Office Action. This Notice indicated the Draftsperson had objected to the drawings submitted on October 3, 2000. However, formal drawings were filed on February 1, 2002, which have not been considered by the Draftsperson. Attached hereto is another set of formal drawings as filed on February 1, 2002, along with a copy of the postcard receipt. It is believed that the drawings submitted on February 1, 2002, are in compliance with the requirements under 37 C.F. R. 1.84 or 1.152. However, if the Examiner requires a resubmission of the formal drawings, the Examiner is requested to contact the Applicants' attorney. Withdrawal of this objection

is respectfully requested.

The Specification

The Examiner has requested that Applicants update the specification to reflect the current status of prior parent applications. Applicants have amended the specification to accommodate this request.

The Information Disclosure Statement

In the Office Action at page 2, the Examiner indicated that the listing of references in the specification is not a proper information disclosure statement (IDS) under 37 CFR 1.98(b). According to the Examiner that unless the references have been cited by the Examiner on forms PTO-892, they have not been considered.

The Examiner's attention is directed to Applicants IDSs filed on April 3, 2001, January 31, 2002, and April 19, 2002. Applicants acknowledge receipt of the Examiner-initialed forms PTO-1449s which were filed together with Applicants IDSs on April 3, 2001 and January 31, 2002. However, the form PTO-1449 filed with Applicants' IDS filed on April 19, 2002, has not been initialed and returned by the Examiner. A duplicate copy of this IDS and postcard receipt is submitted herewith for consideration by the Examiner.

Applicants believe that these previously filed IDSs are in full compliance under 37 CFR 1.98(b) and therefore proper. However, if the Examiner disagrees, the Examiner is respectfully requested to further clarify this objection regarding the information disclosure statements.

The Oath and Declaration

The Examiner has alleged that the Declaration is defective because it does not identify the city and state of residence of each inventor (Office Action, page 3). An executed supplemental declaration in compliance with 37 CFR 167(a) will be provided following this reply. Withdrawal of this objection is respectfully requested.

Objection to the Claims

The Examiner has objected to claims 14, 17, and 20 because the claims refer to the amino acid residue Tyrosine as "Try" rather than "Tyr" (Office Action, page 3). Applicants have amended claims 14, 17 and 20 to properly recite "Tyr" and to correct this inadvertent typographical error. Withdrawal of this objection is respectfully requested.

The Examiner further objected to claims 11-20 because the claims allegedly depend from rejected claims (Office Action, page 3). However, claims 11-20 do not currently depend on the rejected claims. Moreover, the rejections have been rendered moot. Withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 3-5, 8 and 10 under 35 U.S.C. §112, second paragraph as allegedly indefinite (Office Action, page 4). Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that claim 3 is indefinite because "it is unclear what other types of polymerases the polymerase of claim 1 or 2 could be referring to such that claim 3 further limits each of these claims" (Office Action, page 4, lines 9-11). Applicants respectfully disagree.

However, in the interest of expediting the prosecution of allowable subject matter, claim 3 has been amended to delete "or RNA" rendering the basis for this rejection moot. Withdrawal of this portion of the rejection is respectfully requested.

The Examiner alleges that claim 4 is indefinite because of the phrase "said polymerase is mesophilic." According to the Examiner, "[i]t is unclear what characteristic of a polymerase would make it mesophilic" (Office Action, page 4, lines 14-15). Applicants respectfully disagree.

In the interest of expediting the prosecution of allowable subject matter, claim 4 has been amended to recite "said polymerase is derived from a mesophilic organism" to further clarify that which is being claimed. Withdrawal of this portion of the rejection is respectfully requested.

The Examiner further alleges that claim 5 is indefinite because of the phrase "mutants, variants, fragments and derivatives thereof." Specifically, the Examiner asks:

> [w]hat is the scope of the term "mutant, variant, fragments, and derivatives thereof"? When does one polymerase ceases to be a mutant, variant and/or derivative of one polymerase and become a ". . . mutant, variant and/or derivative of a different polymerase.["] Expansion of this argument raises the issue that it is unclear if any or all known polymerases, both DNA, RNA and those yet to be discovered would not be considered a mutant, variant or derivative of one or all the polymerases listed in claim 5, such that claim 5 does not further limit claim 3.

Office Action, page 4, line 18 through page 5, line 2. Applicants respectfully but

emphatically disagree.

Claim 5 has been amended to delete the terms "variants" and "derivatives" rendering this portion of the rejection moot.

The metes and bounds of mutants and fragments of said polymerase are clearly discernible to those skilled in the art in light of the functional and structural limitations of the polymerases set forth in claims 1 and 2. In addition, it is clear that one of ordinary skill in the art can readily achieve mutants and fragments of the claimed invention using teachings of the specification at pages 21-25 and 36-53 and applying routine experimentation. Therefore, claim 5 clearly comports with the requirements under 35 U.S.C. §112, second paragraph. Withdrawal of this portion of the rejection is respectfully requested.

The Examiner alleges that claim 8 is indefinite because of the phrase "discriminatory activity." (Office Action, page 5). Applicants have amended claim 8 to recite "discriminatory activity against one or more dideoxynucleotides" to further clarify that which is being claimed. Therefore, withdrawal of this portion of the rejection is respectfully requested.

The Examiner also alleges that claim 10 is indefinite because of the phrase "the O-helix of said polymerase." According to the Examiner, "[w]hile applicants may teach a number of such O-helixes of a number of known polymerases, it is unclear what in addition to that region of the polymerase defined by SEQ ID NO:1, would be considered to be encompassed by the O-helix of a specific polymerase" (Office Action, page 5, lines 8-11). Applicants respectfully but emphatically disagree.

Claim 10 has been cancelled rendering this portion of the rejection moot.

However, because the rejection may be applied to the presently pending claims, Applicants present the following arguments.

The O-helix region typically defines the nucleotide binding domain of DNA polymerases. It is already known to those of ordinary skill in the art that all polymerases must bind to DNA to function as polymerases. Thus, this region is highly conserved between species of DNA and RNA polymerases as taught by the specification. *See*, for example, the table at page 20. However, positions of the O-helix domain may vary from species to species as exemplified in the specification at page 20. It would be well within the skill of an ordinary skilled artisan to deduce other equivalent regions of polymerase O-helix domains based on the disclosure of the specification. Therefore, one of ordinary skill in the relevant art clearly understands the metes and bounds of what constitutes an O-helix domain of a polymerase. Thus, the claim comports with the requirement of 35 U.S.C. §112, second paragraph. Withdrawal of this portion of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-10 and 37-40 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention (Office Action, pages 5). Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that:

> [t]he specification only provides the representative species encompassed by these claims, wherein the Tne DNA

> polymerase consists of a combination of the following mutations: those mutants having an increase or enhancement of fidelity, consisting of mutation Arg^{722} or Lys^{726}. There is no disclosure of any particular structure to function/activity relationship in the claimed genus. The specification also fails to describe additional representative species of these DNA polymerases by any identifying structural characteristics or properties other than having increased or enhanced fidelity, reduced 3'[-]5' exonuclease activity of the polymerase, reduced 5'[-]3' exonuclease activity or reduced discriminatory behavior against dideoxynucleotides for which no predictability of structure is apparent.

Office Action, page 6, lines 11-21. Applicants respectfully but emphatically disagree.

The specification clearly discloses structural regions of the O-helix domains for different DNA and RNA polymerases at page 20. The specification further teaches and exemplifies how to generate mutations of polymerases for enhanced fidelity, reduced 3'-5' and/or 5'-3' exonuclease activities, and/or reduced discriminatory activity against dideoxynucleotides. *See* specification at pages 21-25, 36-53, and Figure 5. Therefore, it is clear from the disclosure of the specification that Applicants have possession of what is being claimed. Thus, withdrawal of this rejection is respectfully submitted.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-6 and 9 under 35 U.S.C. 102(b) as allegedly anticipated by Barnes (U.S. Patent No. 5,436,149, hereinafter as "Barnes") (Office Action, page 7). Applicants respectfully traverse this rejection.

According to the Examiner, Barnes "teach[es] the Thermus aquaticus DNA polymerase mutant Klentaq-278 which has an increased fidelity thereby reducing its misincorporation of nucleotides, relative to the wildtype enzyme (column 6, lines 19-35). The DNA polymerase mutant taught by Barnes further comprises a mutation in the 5'-3'

exonuclease activity of the polymerase" (Office Action, page 7, lines 16-21). Applicants respectfully disagree.

Claims 1 and 2, and their respective dependent claims, are directed to a nucleic acid polymerase which has been modified to increase or enhance fidelity or to reduce or eliminate misincorporation of nucleotides during nucleic acid synthesis, wherein said modification corresponds to amino acid position Arg722, or Lys726, or Arg722 and Lys726 of a *Thermotoga neopolitana* polymerase. Claims 37-40 further recite a kit for amplifying, synthesizing or sequencing a DNA molecule comprising one or more of said polymerases.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). This burden is not met by the disclosure of Barnes. Barnes does not teach the polymerase as claimed. Therefore, the claims are not anticipated by Barnes. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 37-40 under 35 U.S.C. 103(a) as allegedly unpatentable over Barnes, cited *supra*. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that "[o]ne of ordinary skill in the art at the

time of filing would have been motivated to combine the polymerase taught by Barnes with the additional components needed for the methods taught by Barnes . . . so that the practice of the taught methods would be made more convenient and easier. The reasonable expectation of success of the combining of the necessary components of the taught methods is high based on the high degree of knowledge in the art" (Office Action, page 8, last full paragraph). Applicants respectfully disagree.

Claims 1 and 2, and their respective dependent claims, are directed to a nucleic acid polymerase which has been modified to increase or enhance fidelity or to reduce or eliminate misincorporation of nucleotides during nucleic acid synthesis, wherein said modification corresponds to amino acid position Arg722, or Lys726, or Arg722 and Lys726 of a *Thermotoga neopolitana* polymerase. Claims 37-40 further recite a kit for amplifying, synthesizing or sequencing a DNA molecule comprising one or more of said polymerases.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Specifically, there must be a reason, suggestion, or motivation in the cited art that would motivate one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir.

1988).

This burden has not been met by the disclosure of Barnes. Barnes does not suggest or contemplate a kit for amplifying, synthesizing or sequencing a DNA molecule comprising a polymerase which has been modified to increase or enhance fidelity or to reduce or eliminate misincorporation of nucleotides during nucleic acid synthesis, wherein said modification corresponds to amino acid position Arg722, or Lys726, or Arg722 and Lys726 of a *Thermotoga neopolitana* polymerase. The Examiner has not provided any evidence of the alleged general knowledge in the art that would lead one to Applicants' invention. Therefore, this rejection is in error. Withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond

Robert W. Esmond
Attorney for Applicants
Registration No. 32,893

Date: Sept 23, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Specification:

Please substitute the following paragraph for the pending paragraph at page 1, lines 3-6.

This application is a continuation of Application No. 09/141,522, filed August 27, 1998, now abandoned, which claims the benefit of the filing dates of U.S. Provisional Application Nos. 60/056,263, filed August 29, 1997; 60/060,131, filed September 26, 1997; and 60/085,247, filed May 13, 1998; the disclosures of all of which are incorporated by reference herein in their entireties.

In the Claims:

Claims 10, 13, 16, 19, 21-36, and 41-42 have been cancelled.

New claims 43-64 are sought to be added.

The following claims have been amended:

1. (Once amended) A nucleic acid polymerase which has been modified [or mutated] to increase or enhance fidelity, wherein said modification corresponds to amino acid position Arg722, or Lys726, or Arg722 and Lys726 of a *Thermotoga neopolitana* polymerase.

2. (Once amended) A nucleic acid polymerase which has been modified [or mutated] to reduce or eliminate misincorporation of nucleotides during nucleic acid synthesis, wherein said modification corresponds to amino acid position Arg722, or Lys726, or Arg722 and Lys726 of a *Thermotoga neopolitana* polymerase.

3. (Once amended) The polymerase of claim 1 or 2, wherein said polymerase is a DNA [or RNA] polymerase.

4. (Once amended) The polymerase of claim 3, wherein said polymerase is derived from a mesophilic organism or said polymerase is thermostable.

5. (Once amended) The polymerase of claim 3, wherein said polymerase is selected from the group consisting of *Tne* DNA polymerase, *Taq* DNA polymerase, *Tma* DNA polymerase, *Tth* DNA polymerase, *Tli* (VENT™) DNA polymerase, *Pfu* DNA polymerase, DEEPVENT™ DNA polymerase, *Pwo* DNA polymerase, *Bst* DNA polymerase, *Bca* DNA polymerase, *Tfl* DNA polymerase, and mutants[, variants,] and fragments[, and derivatives] thereof.

6. (Once amended) The polymerase of claim 1 or 2, further comprising one or more modifications [or mutations] to reduce or eliminate one or more activities selected from the group consisting of:

(a) the 3′→5′ exonuclease activity of the polymerase;

(b) the 5′→3′ exonuclease activity of the polymerase; and

(c) the discriminatory activity against one or more dideoxynucleotides.

7. (Once amended) The polymerase of claim 1 or claim 2, wherein said polymerase is modified [or mutated] to reduce or eliminate 3′→5′ exonuclease activity.

8. (Once amended) The polymerase of claim 1 or claim 2, wherein said polymerase is modified [or mutated] to reduce or eliminate discriminatory activity against one or more dideoxynucleotides.

9. (Once amended) The polymerase of claim 1 or claim 2, wherein said polymerase is modified [or mutated] to reduce or eliminate 5′→3′ exonuclease activity.

11. (Once amended) The polymerase of claim [10] 1, wherein said modification is in an O-helix of said polymerase [is defined as RXXXKXXXFXXXYX (SEQ ID NO:1), wherein X is any amino acid].

12. (Once amended) The polymerase of claim [11] 1 or claim 2, wherein said [mutation or] modification corresponds to amino acid [is at] position R (Arg722) [of said O-helix].

14. (Once amended) The polymerase of claim [13] 12, wherein R (Arg722) is substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, [Try] Tyr and Val.

15. (Once amended) The polymerase of claim [11] 1 or claim 2, wherein said [mutation or] modification corresponds to amino acid [is at] position K (Lys726)[of said O-helix].

17. (Once amended) The polymerase of claim [16] 15, wherein K (Lys726) is substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, [Try] Tyr and Val.

18. (Once amended) The polymerase of claim [11] 1 or claim 2, wherein said [mutations or] modifications correspond to amino acid [are] at position R (Arg722) and at position K (Lys726)[of said O-helix].

20. (Once amended) The polymerase of claim 18, wherein R (Arg722) is substituted with an amino acid selected from the group consisting of Ala, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, [Try] Tyr and Val, and wherein K (Lys726) is substituted with an amino acid selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Met, Phe, Pro, Ser, Thr, Trp, [Try] Tyr and Val.